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(57) Abstract

A pharmaceutical preparation comprising a stable, surface-active emulsion or dispersion of a pharmaceutical agent incorporated into an emulsion (i) having a hydrophobic discontinuous phase of a long chain carboxylic acid or ester or alcohol thereof dispersed in an aqueous phase or (ii) having a hydrophilic discontinuous phase dispersed in a hydrophobic phase of a long chain carboxylic acid or alcohol thereof. The emulsion with pharmaceutical agent is incorporated into a pharmaceutical carrier suitable for oral delivery.

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EMULSIFIED DRUG DELIVERY SYSTEMS

The ability of drugs to be administered via the oral route depends on several factors. The drug must be soluble in the gastrointestinal fluids in order for the drug to be transported across biological membranes, or be suitable for an active transport mechanism. Very small particulates (less than 300 nanometers) can be absorbed through the lymphatic system via the Peyer's Patch system in the intestinal tract. However, this mechanism is not capable of absorbing large doses of drugs into the systemic circulation.

A problem arises for hard to dissolve drugs. In the case of conventional drugs, some drugs are relatively insoluble in gastrointestinal fluids. If the extent of solubility is low, this may cause incomplete and/or erratic absorption. If the rate of solubility is low, then absorption will most probably be erratic on an intra-patient and inter-patient basis. Peptide drugs can be water soluble, and these are not as problematic as insoluble peptides. Like conventional drugs, insoluble peptides typically exhibit incomplete or low extent of absorption and erratic absorption or bioavailability.

The primary difficulty involved in delivering peptides orally is their degradation by hydrolysis and proteolytic enzymes. There are two basic approaches to eliminating this difficulty. The first is an "enteric" coating that releases the drug only in neutral to basic pH (usually pH 6-8), like that found in the intestine, so that the peptide is not exposed to gastric juices. However, this approach alone is not sufficient to protect the peptide since proteolytic enzymes exist in the upper intestinal tract, and degradation of the drug can still occur. The other approach is to incorporate the peptide in a hydrophobic material so that aqueous fluids cannot penetrate the system. It is important to select a hydrophobic material that can erode or slowly dissolve in the intestinal tract so that the drug is released. In this way, the peptide is protected from proteolytic enzymes. In addition, it is possible to combine the two approaches. See, for example, with relation to the enteric coating approach.

However, there are inherent difficulties with the approaches outlined above. First, many drugs are released too slowly from hydrophobic systems. Also, some peptides will partition into the hydrophobic phase so that they will not be fully released from these systems. Thus, both the rate and extent of drug release are crucial components of any drug delivery system, and are even more important for many peptide drugs.

In accordance with the present invention there is provided a pharmaceutical composition comprising a pharmaceutical agent incorporated into a pharmaceutical carrier emulsion comprised of a hydrophobic material selected from the group consisting of a long chain carboxylic acid, long chain carboxylic acid ester, long chain carboxylic acid

alcohol and mixtures thereof emulsified with a hydrophilic material.

The composition is used for convenient delivery of drugs. A wide range of active agents can be administered in the composition, including antibiotics, antimicrobials, antineoplastics, antivirals, cardiovascular and renal agents, immunosuppressive and immunostimulatory agents, and CNS active agents, but it is of particular value for peptides. Microemulsion, compared with normal (macro-) emulsions, form easily, even spontaneously, without high energy input, and scale-up easily. They are stable, with long shelf life, and, being translucent, are easy to monitor spectroscopically. They have low viscosity for easy transport and mixing. Drug solubilization, protection against enzyme hydrolysis and, therefore, oral bioavailability, particularly for peptides, are enhanced.

In one embodiment, the hydrophobic material forms the discontinuous phase and the hydrophilic material forms the continuous phase in which the hydrophobic material is emulsified (oil-in-water). The hydrophobic discontinuous phase and the hydrophilic continuous phase can each independently be solid, semisolid or liquid. The pharmaceutical agent may be dispersed or incorporated into the hydrophobic material, the hydrophilic material or in both the hydrophobic and hydrophilic materials. Preferably the carrier emulsion is a microemulsion.

In another embodiment, the hydrophobic material forms the continuous phase and the hydrophilic material forms the discontinuous phase in which the hydrophobic material is emulsified(water-in-oil). The hydrophobic discontinuous phase and hydrophilic continuous phase can each independently be solid, semisolid or liquid. The pharmaceutical agent may

be dispersed or incorporated into the hydrophobic material, the hydrophilic material or in both the hydrophobic and hydrophilic materials. Preferably the carrier emulsion is a microemulsion. In this embodiment the invention provides a pharmaceutical preparation comprising a water-in-oil emulsion, preferably a microemulsion, containing an oil phase (such as a long chain carboxylic acid or ester or alcohol thereof), a surface active agent (such as poloxamer) and an aqueous phase containing the drug. The advantage of using a water-in-oil microemulsion is that it has the ability to dissolve relatively large amounts of polar solutes in an overall oily environment, creating an oral delivery system for peptide and protein drug molecules.

Figure 1 shows the results of the experiments described in Example 8.

Figure 2 shows the results of the experiments described in Example 9.

Figure 3 shows the results of the experiments described in Example 10.

Figure 4 shows the results of the experiments described in Example 11.

Figure 5 shows the results of the experiments described in Example 12.

An emulsion is a dispersed system containing at least two immiscible liquid phases, a hydrophobic phase and a hydrophilic phase. The emulsion comprises the dispersed phase, the dispersion phase and an emulsifying agent or surfactant agent, except when the hydrophobic material is a "self-emulsifying" ester, whereby it is possible to produce

an emulsion without a separate emulsifying agent. Usually one of the two immiscible liquids is an oil while the other is aqueous. Which phase becomes the dispersed phase depends on the relative amounts of the two liquid phases and which emulsifying agent is selected. Therefore, an emulsion in which the oil is dispersed as droplets throughout the aqueous phase is called an oil-in-water (o/w) emulsion and vice versa. The term "colloidal" refers to emulsions in which the dispersed phase is of very fine particles, usually less than about 1 mm in size. A "microcolloid" is an emulsion wherein the dispersed particles are usually about 100 um or less in size. Cosurfactants are also common components of microcolloids and are simply surfactants included in addition to the primary surfactant.

A "microemulsion" is an optically isotropic and thermodynamically or kinetically stable liquid emulsion. Microemulsions are composed of an oily phase, an aqueous phase, a surfactant and sometimes a cosurfactant. They are ideal for oral drug delivery systems since they are homogeneous, thermodynamically stable, have uniform droplet sizes of approximately 200Å and are optically clear. A water-in-oil microemulsion, in particular, has small aqueous phase droplets, uniformly dispersed in a continuous oil phase. Therefore, over a wide range of peptide solubilities the peptide is protected from proteolytic enzymes that are soluble in the digestive fluids. In general, the chemical structure of peptides dictates that they be at least somewhat if not mostly water soluble, and thus will be located inside the water droplet or very near the surface of the droplet of the water-in-oil microemulsion system. Thus, the outer oily phase of the microemulsion will prohibit migration of proteolytic enzymes through the delivery system. The outer oily phase of the microemulsion is also able to incorporate into the intestinal cell matrix, thus creating channels

(either para cellularly or transcellularly) through which the peptide drug could pass.

Therefore it is important to select a hydrophobic material that can erode or slowly dissolve in the intestine or become incorporated into the intestinal cell matrix so that the drug is released. In addition, it is possible to combine the two approaches, for example, with relation to the enteric coating approach.

The oil-in-water emulsions of the invention are generally made by adding hot (70-80° C) hydrophobic phase (smaller by weight) to hot (70-80° C) hydrophilic phase (larger by weight) forcing inversion of the surface active agent to form a disperse emulsion of unaggregated dispersed phase particles. This produces an emulsion when processed under suitable shear. The drug is usually added with the hydrophobic material when it is an organic molecule that is poorly soluble in aqueous media. The drug is usually added after the emulsion has been formed and allowed to cool when it is a peptide. The drug in emulsion formulation is then filled into a soft or hard gelatin capsule, tablet or other oral dosage form.

In accordance with the present invention certain hydrophobic materials, when emulsified in a continuous phase of a hydrophilic material provide enhanced absorption capabilities for oral delivery of peptide drugs and drugs that are poorly soluble in aqueous media. In accordance with the invention, these materials are selected from the group consisting of long chain carboxylic acids, long chain carboxylic acid esters, long chain carboxylic acid alcohols and mixtures thereof.

Further, certain materials, when combined in accordance with the invention to form a water-in-oil microemulsion, give enhanced absorption capabilities. These materials are an oily phase, composed of long chain fatty acids or esters or alcohols thereof, an aqueous phase composed primarily of water, and a surface active agent, primarily of the non-ionic block copolymer type, that are mixed together to form a water-in-oil microemulsion.

The long chain carboxylic acids, generally contain from 4-36 carbon atoms and preferably contains at least 12 carbon atoms, most preferably 12 to 22. In some cases this carbon chain is fully saturated and unbranched, while others contain one or more double bonds. They can have saturated, unsaturated, branched or straight chain hydrocarbon chains. A few contain 3-carbon rings or hydroxyl groups. The compounds are not surface active. They are poorly soluble in water and the longer the acid chain and the fewer the double bonds, the lower the solubility in water. The carboxylic acid group is polar and ionized at neutral pH. This accounts for the slight solubility of short-chain acids in water.

Examples of such acids are those ranging from C_{16} to C_{22} with up to three unsaturated bonds (also branching). Examples of saturated straight chain acids are n-dodecanoic acid, n-tetradecanoic acid, n-hexadecanoic acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, montanic acid and melissic acid. Also useful are unsaturated monoolefinic straight chain monocarboxylic acids. Examples of these are oleic acid, gadoleic acid and erucic acid. Also useful are unsaturated (polyolefinic) straight chain monocaboxyic acids. Examples of these are linoleic acid, ricinoleic acid, linolenic acid, arachidonic acid and

behenolic acid. Useful branched acids include, for example, diacetyl tartaric acid.

Examples of long chain carboxylic acid esters include, but are not limited to, those from the group of: glyceryl monostearates; glyceryl monopalmitates; mixtures of glyceryl monostearate and glyceryl monopalmitate (Myvaplex 600, Eastman Fine Chemical Company); glyceryl monolinoleate; glyceryl monooleate; mixtures of glyceryl monopalmitate, glyceryl monostearate, glyceryl monooleate and glyceryl monolinoleate (Myverol 18-92, Eastman Fine Chemical Company); glyceryl monolinolenate; glyceryl monogadoleate; mixtures of glyceryl monopalmitate, glyceryl monostearate, glyceryl monooleate, glyceryl monolinoleate, glyceryl monolinolenate and glyceryl monogadoleate (Myverol 18-99, Eastman Fine Chemical Company); acetylated glycerides such as distilled acetylated monoglycerides (Myvacet 5-07, 7-07 and 9-45, Eastman Fine Chemical Company); mixtures of propylene glycol monoesters, distilled monoglycerides, sodium stearoyl lactylate and silicon dioxide (Myvatex TL, Eastman Fine Chemical Company); mixtures of propylene glycol monoesters, distilled monoglycerides, sodium stearoyl lactylate and silicon dioxide (Myvatex TL, Eastman Fine Chemical Company) d-alpha tocopherol polyethylene glycol 1000 succinate (Vitamin E TPGS, Eastman Chemical Company); mixtures of mono- and di-glyceride esters such as Atmul (Humko Chemical Division of Witco Chemical); calcium stearoyl lactylate; ethoxylated mono- and di-glycerides; lactated mono- and di-glycerides; lactylate carboxylic acid ester of glycerol and propylene glycol; lactylic esters of long chain carboxylic acids; polyglycerol esters of long chain carboxylic acids, propylene glycol mono- and di-esters of long chain carboxylic acids; sodium stearoyl lactylate; sorbitan monostearate; sorbitan monooleate; other sorbitan esters of long chain carboxylic acids; succinylated monoglycerides; stearyl

monoglyceryl citrate; stearyl heptanoate; cetyl esters of waxes; stearyl octanoate; C_{10}-C_{30} cholesterol/lavosterol esters; and sucrose long chain carboxylic acid esters.

Examples of the self-emulsifying long chain carboxylic acid esters include those from the groups of stearates, palmitates, ricinoleates, oleates, behenates, ricinolenates, myristates, laurates, caprylates, and caproates.

The alcohols useful in the invention are exemplified by the hydroxyl forms of the carboxylic acids exemplified above and also stearyl alcohol.

Additives to the carboxylic acid/alcohol phase can be used to create a solid at room temperature. This addition affords the opportunity to make better use of enteric coatings. Examples of such additives are glycerol behenate, cetyl alcohol, stearic acid, sorbitan ester derivatives such as sorbitan stearate, sobitan isostearate, polyethylene glycol 1000 to 6000.

The types of protective or sustained release coatings that can be used include, but are not limited to, ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose and esters of methacrylic and ethacrylic acid (Eudragit RL, RS, and NE polymer products, Rohm Pharma, Darmstadt, Germany). The enteric protective materials or coatings can be, for example, cellulose acetate pthalate, hydroxypropylmethylcellulose pthalate, ethylvinylacetate pthalate, polyvinylacetate pthalate and esters of methacrylic and ethacrylic acid (Eudragit S, Eudragit L and Eudragit E30D, Rohm Pharma, Darmstadt, Ger.).

The composition or preparation of the invention can further include a surfactant, or a mixture of two or more surfactants. A surfactant is an amphiphilic molecule consisting of a hydrophobic tail and a hydrophilic head. These molecules possess distinct regions of both hydrophilic and hydrophobic character. The hydrophobic tail can be a hydrocarbon or fluorocarbon chain of 8 to 18 carbon atoms. They are long chain molecules such as, for example, soaps or detergents. Surfactants accumulate at the hydrophilic/ hydrophobic (water/oil) interface and lower the surface tension. Surface active agents or surfactants are long chain molecules, such as soaps and detergents, which accumulate at the hydrophilic/hydrophobic(water/oil) interface and lower the surface tension at the interface. One effect of a reduced surface tension is the stabilization of the emulsions. This is because molecules with both polar and non-polar groups become oriented such that the hydrocarbon tail embeds itself into the hydrophobic phase and the hydrophilic head protrudes into the hydrophilic phase. Where the hydrophobic composition or other component of the preparation includes a surface-active agent, such as a surfactant, it is usually present in amounts of about 0.05% to 50.0% weight/weight of the hydrophobic composition with a preferred range of 1.0% to 3.0% (w/w). Preferred surfactants include, for example, the Tween(polyoxyethylene sorbate) family of surfactants(ICI, Wilmington DE), the Span(sorbitan long chain carboxylic acid esters) family of surfactants(ICI), the Pluronic(ethylene or propylene oxide block copolymers) family of surfactants(BASF, Parsippany NJ), the Labrasol, Labrafil and Labrafac(each polyglycolyzed glycerides) families of surfactants(Gappe Fosse, St. Priest, France), sorbitan esters of oleate, stearate, laurate or other long chain carboxylic acids, poloxamers (polyethylene-polypropylene glycol block copolymers), other sorbitan or sucrose long chain carboxylic acid esters, mono and

diglycerides, PEG derivatives of caprylic/capric triglycerides and mixtures thereof.

The drugs to be incorporated individually or as combinations in the pharmaceutical preparations of the invention are those having less than about 80% oral bioavailability. The term "bioavailability" as used here means the rate and extent of systemic absorption of a drug from the oral route of administration.

In one aspect, the drug is a polypeptide, usually of less than about 15 amino acids. Examples include cyclosporin, angiotensin I, II and III, encephalins, enkephalins and their analogs, ACTH, antiinflammatory peptides I, II, III, bradykinin, calcitonin, cholecystikinin (CCK) fragments 26-33 and 30-33, pre/pro CCK (V-9-M), ß-endorphin, dinorphin, leucokinin, leutinizing hormone releasing hormone (LHRH), neurokinins (e.g. neurokinin A), somatostatin, substance P, thyroid releasing hormone (TRH), vasopressin, fibrinogen receptor antagonists (arginine-glycine-aspartic acid containing peptides) which are platelet aggregation inhibitors, growth hormone releasing peptides (GHRP), insulin, LH-RH releasers and inhibitors, endothelins, artial natreutetic factor, gastrin, cytoprotectives, MSH modulators, or elastase or growth factors and cytokines, renin inhibitors, and HIV protease inhibitors.

In another aspect, the drug is an organic molecule that is poorly soluble in aqueous media. These organic molecules usually have a molecular weight (m.w.) of less than about 1,000 daltons, and usually less than about 600 daltons. Examples include cabamazepine, griseofulvin, angiotensin converting enzyme inhibitors, flutamide, nifedipine, acyclovir, gancyclovir, indomethacin, naproxen, estrogens,

testosterones, steroids, phenytoin, ergotamines and cannabinoids.

Preferred drugs that meet these criteria include, but are not limited to, angiotensin I, II and III, ACTH, anti-inflammatory peptides 1, 2 and 3, bradykinin, cyclosporin, calcitonin, CCK fragments 26-33 and 30-33, Pre- pro-CCK (V-9-M), beta-endorphin, dynorphin, leucokinin, LHRH, neurokinin A, somatostatin, substance P, TRH, vasopressin, enkephalin analogues, ebiratide, galanin, and growth hormone releasing hormone.

In accordance with the invention, drugs are incorporated into the microemulsions by admixture using conventional mixing devices and homogenizers used for semi-solid ointments and lotions, with agitation at speeds common to emulsified products such as creams and emulsions. Examples of common equipment employed are propeller or turbine mixers, homogenizers, colloid mills, ultrasonic mixers and microfluidizers. Examples of such brand name mixing equipment are Lee Kettle, Gaulin mixer and Stephan. The shear of the agitation should be sufficient to form a stable dispersion, but not too great to cause degradation of the drug. The shear forces will form aggregates that have diameters ranging from 100 - 500 angstroms. Suitable homogenizers are available from Micromedics, Inc., Silverson, and APV Crepaco, Arde Barinco. Stephen and Fryma mixers can also be employed with suitable vacuum to prevent formation of bubbles. Monitoring and evaluation of pH, viscosity, specific gravity and aggregate sizes are necessary.

Using these devices, the mixture of drug in the hydrophobic material (in the oil-in-water embodiment) is formed into particles, e.g. beads or spheres, by spray-congealing or "prilling". This process uses a spray nozzle

which atomizes the material in a cooling tower or chamber. As the material is sprayed, surface tension causes a uniform spherical bead to be formed. As the bead falls through the cooling chamber, it hardens into a stable, intact sphere.

The particles generally have a particle size of from 0.5 microns to 100 microns. It is preferred to reduce the size of the sphere as much as possible, most preferably below 10 microns. Optionally, the particles are coated with a sustained-release coating and/or an enteric coating to modify the rate of drug release from the particles.

The particles can be incorporated into hard gelatin capsules, either with additional excipients, or alone. Typical excipients to be added to a capsule formulation include, but are not limited to: fillers such as microcrystalline cellulose, soy polysaccharides, calcium phosphate dihydrate, calcium sulfate, lactose, sucrose, sorbitol, or any other inert filler. In addition, there can be flow aids such as fumed silicon dioxide, silica gel, magnesium stearate, calcium stearate or any other material imparting flow to powders. Because of their hydrophobic nature, the particles should not need a lubricant, but one can be added if necessary by using polyethylene glycol, leucine, glyceryl behenate, magnesium stearate or calcium stearate.

The particles may also be incorporated into a tablet, in particular by incorporation into a tablet matrix, which rapidly disperses the particles after ingestion. In order to incorporate these particles into such a tablet, a filler/binder must be added to a tablet that can accept the particles, but will not allow their destruction during the tableting process. Materials that are suitable for this purpose include, but are not limited to, microcrystalline

cellulose (Avicel), soy polysaccharide (Emcosoy), pre-gelatinized starches (STARCH 1500, National 1551), and polyethylene glycols (Carbowax). The materials should be present in the range of 5-75% (w/w), with a preferred range of 25-50% (w/w).

In addition, disintegrants are added in order to disperse the particles once the tablet is ingested. Suitable disintegrants include, but are not limited to: cross-linked sodium carboxymethyl cellulose (Ac-Di-Sol), sodium starch glycolate (Explotab, Primojel), and cross-linked polyvinylpolypyrrolidone (Plasdone-XL). These materials should be present in the range of 3-15% (w/w), with a preferred range of 5-10% (w/w).

Lubricants are also added to assure proper tableting, and these can include, but are not limited to: magnesium stearate, calcium stearate, stearic acid, polyethylene glycol, leucine, glyceryl behanate, and hydrogenated vegetable oil. These lubricants should be present in amounts from 0.1-10% (w/w), with a preferred range of 0.3-3.0% (w/w).

Tablets are formed, for example, as follows. The particles are introduced into a blender along with Avicel, disintegrants and lubricant, mixed for a set number of minutes to provide a homogeneous blend which is then put in the hopper of a tablet press with which tablets are compressed. The compression force used is adequate to form a tablet; however, not sufficient to fracture the beads or coatings.

The capsule or tablet can also be enteric coated. Either the particles can be enteric coated (Ph sensitive) and released in the stomach or the capsule or tablet can be enteric coated (thereby releasing the particles in the

intestine), in which case the particles need not be so coated. To use only a sustained release coating on the particle one would also need an enteric coated capsule or tablet. There are three approaches here. First, there is the uncoated hydrophobic particle in an enteric coated capsule. Second, there is the sustained release coated particle within an enteric coated capsule or tablet. Third, there is the enteric coated particle enclosed within a regular soft gelatin capsule or uncoated tablet.

The capsule may be further processed to provide gastric protection by enterically coating the capsule. When the contents of the capsule are released into the gastrointestinal milieu, it spontaneously forms a microcolliodal emulsion with the gastrointestinal fluid. The gastrointestinal fluid acting as the aqueous phase.

Microemulsions are generally formed by adding the aqueous phase, oily phase, and surfactant to a suitable vessel and mixing. If any of the ingredient is a solid, it should be added to a liquid phase in which it is soluble and heated to dissolve. For example, if the surfactant is a solid, and it is soluble in the oily phase, then it should be dissolved completely, then followed with aqueous phase, etc. On the other hand, if the surfactant is soluble in the aqueous phase, then it should first be added to the aqueous phase, dissolved completely, followed by the oily phase. Appropriate mixing devices as mentioned above can be employed for this purpose.

The preparation of an oil-in-water emulsion based system, requires that the drug be dispered into the hydrophobic material as described above, with the aqueous phase being added in the presence of surfactant or self-emulsifying hydrophobic long chain carboxylic acid ester.

This procedure under suitable shear forms a microemulsion. This emulsion is then filled into a soft or hard gelatin capsule. The capsule may be further processed to provide gastric protection by enterically coating the capsule.

Examples 1-7 describe formulations that illustrate the oil-in-water embodiment of the invention.

EXAMPLE 1

Phase	Ingredients	%W/W
B	Carbamazepine	5
B	Glyceryl Monostearate	5-60
A	Polysorbate 80	5
A	Oleic Acid	2-10
A	Water	q.s. to 100

The ingredients of each phase are heated separately to 70-80° C. Phase B is added to phase A while mixing in an appropriate mixing device. The mixture is then cooled to room temperature. The resultant emulsion is ready to be incorporated into any suitable oral delivery dosage form.

EXAMPLE 2

Phase	Ingredients	%W/W
B	Cyclosporine	5
B	Medium Chain Mono and Digiycerides	17
A	Polysorbate 80	5
B	Oleyl Alcohol	2-10
A	Water	q.s. to 100

The procedure is the same as that described in Example 1.

EXAMPLE 3

Phase	Ingredients	%W/W
B	ACE Inhibitor	5
A	Peg-25 Glyceryl Trioleate	30-60
B	Oleyl Alcohol	2-10
A	Water	q.s. to 100

The procedure is the same as that described in Example 1.

EXAMPLE 4

Phase	Ingredients	%W/W
B	Somatostatin	5
B	Medium chain Mono and Diglycerides	17
A	Polysorbate 80	5
A	Oleic Acid	2-10
A	Water	q.s. to 100

The procedure is the same as that described in Example 1.

EXAMPLE 5

Phase	Ingredient	%W/W
A	Enkephalin	5
B	Oleyl alcohol	14
C	Sorbitan Monooleate	14
D	Polysorbate 80	14
E	Water	q.s. 100

Phase A and B are mixed together, then C through E are added in any order with stirring.

EXAMPLE 6

Phase	Ingredient	%W/W
A	TRH	5
B	d-Alphatocopheryl Polyethylene glycol 1000 succinate	10
C	d-alpha Tocophenol acetate	3
D	Oleyl alcohol	2-10
E	Water	q.s. 1000

Ingredients B and C are heated to >40° C and mixed. Ingredient A is then added. Ingredient D is then added to the above and the resultant mixture is then added to ingredient E, which is at ~ 70-80°C. This is then mixed while cooling.

EXAMPLE 7

Phase	Ingredient	%W/W
A	Ebiratide	5
B	Acetylated monoglycerides	10
C	Dioctyl sodium sulfosyccinate	10
D	Apricot Kernal oil	10
E	Water	q.s. 100

Phase A is dissolved into D, then the other ingredients are added with gentle stirring.

Examples 8-12 describe formulations that illustrate the water-in-oil embodiment of the invention and demonstrate *in vitro* delivery enhancement across Caco-2 cells using the model peptide DAGO enkephalin.

Preparation of Caco-2 Cells

An *in vitro* model of intestinal epithelium, the Caco-2 human colon carcinoma cell line is used as the preliminary assay system. These cells differentiate in culture to form a confluent monolayer with the barrier properties of normal

intestinal epithelium. Cells are grown on permeable membranes in a transport system with discrete, accessible liminal and basil compartments.

The time course of differentiation, barrier formation, and active transport of glucose has been determined. Cells have been found to form brush borders and tight junctions between cells as demonstrated by electron microscopy, enzyme assays, and reversible opening of calcium dependent junctions by chelation. Transport of labeled peptides is measured from luminal to basal compartments with time. Microemulsions are compounded using physiologic buffers vs. the aqueous phase and applied to the luminal surface of the cell monolayer. Appearance of peptides is quantified and percent transport per hour per square centimeter calculated and compared to buffer alone.

Example 8

Ingredients	**%**
Poloxamer 124	27.0
Linoleic acid	63.1
Aqueous phase	9.9

General Procedure

Mix ingredients well using one of the above mentioned appropriate mixing devices in a suitable container to form an optically clear solution. Add 10 mM DAGO enkephalin and apply solution to Caco-2 cells. The results are shown in Figure 1.

Example 9

Ingredients	%
Poloxamer 124	19
Oleyl alcohol	75.9
Aqueous phase	5.1

General Procedure

Mix ingredients well using one of the above mentioned appropriate mixing devices in a suitable container to form an optically clear solution. Add 10 mM DAGO enkephalin and apply solution to Caco-2 cells. The results are shown in Figure 2.

Example 10

Ingredients	%
Poloxamer 124	27.0
Oleic acid	63.1
Aqueous phase	9.9

General Procedure

Mix ingredients well using one of the above mentioned appropriate mixing devices in a suitable container to form an optically clear solution. Add 10 mM DAGO enkephalin and apply solution to Caco-2 cells. The results are shown in Figure 3.

Example 11

Ingredients	%
Poloxamer 124	27.0
Linoleic acid	61.7
Aqueous phase	9.9
Behenic acid	1.35

General Procedure

Melt behenic acid in linoleic in a suitable container at 50-80°C. Cool to 40°C, add remaining ingredients and mix well. Add 10 mM DAGO enkephalin and apply solution to Caco-2 cells. This microemulsion is a solid at room temperature. The results are shown in Figure 4.

Example 12

Ingredients	%
Poloxamer 105	27.0
Linoleic acid	63.1
Aqueous phase	9.9

General Procedure

Mix ingredients well using one of the above mentioned appropriate mixing devices in a suitable container to form an optically clear solution. Add 10 mM DAGO enkephalin and apply solution to Caco-2 cells. The results are shown in Figure 5.

Example 13

Pluronic L44/Fatty Acid or Alcohol/Hank's Microemulsion System for the Transport of Peptides Across Caco-2 Cells

Microemulsion system formulations containing Pluronic L44 as the surfactant, Hank's buffer as the aqueous phase and several possible oily phases: oleyl alcohol, oleic acid, and linoleic acid were prepared.

The following materials were used as received to prepare the formulations: Polysorbate 20, 60 and 80 (Tween 20, 60, and 80, ICI Surfactants, Wilmington DE); glyceryl monooleate/propylene glycol mixture, (Arlacel 186, ICI Surfactants, Wilmington DE); glyceryl monooleate (Aldo MO, Lonza Specialty Chemicals, Fair Lawn, NJ); sorbitan

monooleate (Crill 4, Croda, Parsippany, NJ); oleyl alcohol (Janssen Chemica, Geer, Belgium); and linoleic acid (Emersol 315 Henkel).

Multiple formulations were examined in an effort to utilize the polysorbate surfactant class in a microemulsion vehicle for peptide delivery. The three ICI surfactants Tween 20, 60, and 80 were employed in solution and microemulsion systems with and without cosurfactants. The following present the formulations prepared.

Microemulsion formulations, consisting of Tween 80, Arlacel 186, oleyl alcohol and distilled water and the corresponding Emulsifier (4 parts Tween 80/1 part Arlacel 186) solutions in Hank's buffer were prepared. See Table 1.

TABLE 1

Ingredients	72A(%)	72B1(%)	72B2(%)	B3(%)	B4(%)
Tween 80	28.6	4	8	12	16
Arlacel 186	42.9	1	2	3	4
Distilled Water	25	95	90	85	80

Formulations with a higher percent of Emulsifier (4 parts Tween 80/1 part Arlacel 186) solutions in Hank's buffer were also prepared See Table 2.

TABLE 2

Ingredients	1	2	3	4
Tween 80	16	20	24	28
Arlacel	4	5	6	7
Hank's buffer	80	75	70	65

The formulation for a waterless microemulsion system, consisting of Tween 80, Arlacel 186 and Oleyl alcohol was also prepared. See Table 3.

TABLE 3

Ingredients	%
Tween 80	36.9
Arlacel 186	36.9
Oleyl alcohol	26.1

The formulations for 10% solutions of Tween 20, 60 and 80 in Hank's buffer each at pH 3.5 and 6.5 - 7.0 were prepared. In this case, the peptide incorporated for the is vasopressin at 10 μM. See Table 4.

TABLE 4

Ingredients	F(%)	G(%)	H(%)	I(%)	J(%)	K(%)
Tween 20	10	-	-	10	-	-
Tween 60	-	10	-	-	10	-
Tween 80	-	-	10	-	-	-
Hank's buffer	90	90	90	90	90	90
Ph	6.51	6.91	6.82	3.54	3.4	3.59

The formulation for a waterless microemulsion system, consisting of Tween 20, Arlacel 186 and Oleyl alcohol. (Note different surfactant from formula above). See Table 5.

TABLE 5

Ingredients	72A(%)	72B1(%)	72B2(%)	B3(%)	B4(%)
Tween 80	28.6	4	8	12	16
Arlacel 186	42.9	1	2	3	4
Distilled Water	25	95	90	85	80

Tween 20/Span 20 microemulsion formulations containing linoleic acid as the oily phase were also prepared. See Table 6.

TABLE 6

Ingredients	6A	6B	6C	6D	6E
Tween 20	38.3	42.8	26.3	29	47.5
Span 20	9.6	4.8	2.9	-	-
Linoleic Acid	47.8	47.5	68.1	67.6	47.5
Oleic Acid	-	-	-	-	-
Oleyl Alcohol	-	-	-	-	-
Hank's buffer	4.6	5.1	3	3.6	5.2

Tween 20/Span 20 microemulsion formulations containing either linoleic acid, oleic acid or oleyl alcohol were also prepared. See Table 7.

TABLE 7

Ingredients	6A	6B	6C	6D	6E	13A	13B	13C	13D	13E	14B
Tween 20	38.3	42.8	26.3	29	47.5	38.3	42.8	26.3	29	47.5	38.9
Span 20	9.6	4.8	2.9	-	-	9.6	4.8	2.9	-	-	9.7
Linoleic Acid	47.8	47.5	68.1	67.6	47.5						
Oleic Acid	-	-	-	-	-	47.8	47.5	68.1	67.6	47.5	
Oleyl Alcohol	-	-	-	-	-						48.7
Hank's buffer	4.6	5.1	3	3.6	5.2	4.6	5.1	3	3.6	5.2	2.6

Three additional microemulsion formulations were also prepared. See Table 8.

TABLE 8

Ingredients	A(%)	B(%)	C(%)
Pluronic L44	26.8	-	-

Labrasol	-	38.1	-
Labrafac CM-10	-	9.5	-
Tween 20	-	-	42.8
Span 20	-	-	4.76
Linoleic Acid	63.2	47.6	47.6
Hank's buffer	9.9	4.76	4.76

Further formulation efforts with Tween 20 led to a microemulsion in which Span 20 is the cosurfactant. Span 20, or sorbitan monolaurate, acts as an ideal cosurfactant. The oily phase of the new microemulsion systems has also been changed to linoleic acid or oleic acid, which are known to promote peptide transport in other vehicles. Hank's buffer is the aqueous phase and linoleic acid, oleic acid or oleyl alcohol are the oily phases.

Example 14

Polysorbate Surfactant Systems and Microemulsions in Oral Peptide Delivery.

The primary research initiative has been to screen and identify systems that increase peptide transport across Caco-2 monolayers. One such system explored contains the surfactant Pluronic L44. Several microemulsion systems formulations have been developed using this surfactant. This example summarizes these systems.

The following materials were used as received to prepare the formulations: Pluronic L44 (BASF, Parsippany, NJ); oleyl Alcohol (Jannsen Chemica, Geer, Belgium); oleic acid (Emersol 221, Henkel, Emery Group, Cincinnati, OH); linoleic acid (Emersol 315, Henkel, Emery Group, Cincinnati, OH); and Hank's buffer (Cellgro, Mediatech).

The following tables list formulations prepared for use in transport experiments. The tables give detailed information on the ingredients, amounts and pH, if appropriate.

TABLE 9

Percent Pluronic L44 in Hank's Buffer

		Formulation		
		G	H	I
Ingredient	%	%	%	%
Pluronic L44	0	7.5	15	30.0
Hank's buffer	100	92.5	85.0	70.0

TABLE 10

Formulation of Pluronic Microemulsions

	Formulation	
	D	E
Ingredients	%	%
Pluronic L44	26.8	30
Oleyl alcohol	62.5	70
Hank's	10.7	0

TABLE 11

Microemulsions Containing Pluronic L44, Oleyl Alcohol, Hank's Buffer and Solutions of Pluronic F68 and F108

	Formulations			Ratio Pluronic L44 to Oleyl Alcohol
Ingredients	A	B		
Pluronic L44	27	28.3		3
oleyl alcohol	63.1	66		7

Hank's buffer	9.9	5.7		

Ingredients	C	D	E	
Pluronic L44	41.8	44.76	47.44	5
oleyl alcohol	41.8	44.76	47.44	5
Hank's buffer	16.3	10.47	5.12	

Ingredients	F	RATIO	G	
Pluronic L44	19	2	34.2	4
oleyl alcohol	75.9	8	51.3	6
Hank's buffer	5.1		9.4	

Ingredients	H	I	J	
Pluronic F68	30	15	7.5	
Hank's buffer	70	85	92.5	

Ingredients	L	M	N	
Pluronic F108	15	7.5	3.75	
Hank's buffer	85	9.25	9.625	

TABLE 12

Microemulsions with Pluronic L44 to Oily Phase Ratio of 3:7. Oily phases are either oleic acid or linoleic acid. Percent aqueous phase (Hank's buffer) varies changes from about 10% to about 14%.

Formulation A	%
Pluronic L44	27
oleic acid	63.1
Hank's buffer	9.9

Formulation B	%
Pluronic L44	27

linoleic acid	63.1
Hank's buffer	9.9

Formulation C	%
Pluronic L44	25.8
oleic acid	60.1
Hank's buffer	14.1

Formulation D	%
Pluronic L44	25.8
linoleic acid	60.1
Hank's buffer	14.1

TABLE 12

A) Pluronic L44/linoleic acid/Hank's buffer and B) Pluronic L44/oleic acid/Hank's buffer microemulsions at pH 6.5. The pH was increased using NaOH pellets.

Ingredients	%
Pluronic L44	27
linoleic acid	63.1
Hank's buffer	9.9
NaOH pellets	
pH 6.5	

Ingredients	%
Pluronic L44	27
oleic acid	63.1
Hank's buffer	9.9
NaOH pellets	
pH 6.5	

TABLE 14

Formulations of Pluronic L44/linoleic acid/Hank's buffer at various pH's. The pH was increased using NaOH pellets.

PD0002-9D1

Formulations PD0002-			
Ingredients	9D1	9D2	9D3
Pluronic L44	27	27	27
linoleic acid	63.1	63.1	63.1
Hank's buffer	9.9	9.9	9.9
pH	3.5	4.5-5.0	6.0-6.5

PD0002-9D2: Same As D1, but pH 4.5-5.0

PD0002-9D3: Same As D1, but pH 6.0-6.5

PD0002-9E1

Formulations PD0002-			
Ingredients	9E1	9E2	9E3
Pluronic L44	27	27	27
oleic acid	63.1	63.1	63.1
Hank's buffer	9.9	9.9	9.9
pH	3.5	4.5-5.0	6.0-6.5

PD0002-9E2: Same As E1, but pH 4.5-5.0

PD0002-9E3: Same As E1, but pH 6.0-6.5

TABLE 15

Microemulsion component controls at various pH's: A) Pluronic L44 solutions at pH 2.2, 3.5, 4.8 and 7.9; B) Hank's buffer at pH 2.1, 3.5, 5.0, 7.8; and C) linoleic acid.

A

	Date	
PD0002-10A	5.4.94	26.8% Pluronic L44 in Hank's buffer pH 7.9
PD0002-10B	5.4.94	26.8% Pluronic L44 in Hank's buffer pH 4.8
PD0002-10C	5.4.94	26.8% Pluronic L44 in Hank's buffer pH 3.5
PD0002-10D	5.4.94	26.8% Pluronic L44 in Hank's buffer pH 2.2

B

	Date	
PD0002-11A	5.4.94	100% HANK'S BUFFER pH 7.8
PD0002-11B	5.4.94	100% HANK'S BUFFER pH 5.0
PD0002-11C	5.4.94	100% HANK'S BUFFER pH 2.1
PD0002-11D	5.4.94	100% HANK'S BUFFER pH 3.5

C

	Date	
PD0002-10E	5.4.94	100% LINOLEIC ACID

TABLE 16

Pluronic L44/linoleic acid/Hank's buffer microemulsion at pH 3.5, 5.0 and 7.0.

	PD0002-12		
Ingredients	A	B	C
Pluronic L44	27	26.8	25.5
linoleic acid	63.1	62.6	59.6
Hank's buffer	9.9	9.8	15
pH	3.5-3.8	4.9	7

Example 15

Variations of the Pluronic L44/Linoleic Acid/Hank's Microemulsion System

The following materials were used as received to prepare the formulations: Pluronic L44 (BASF, Parsippany, NJ); linoleic Acid (Emersol 315, Henkel, emery Group, Cincinnati, OH); oleic Acid (Emersol 221, Henkel, Emery Group, Cincinnati, OH); linolenic Acid (Aldrich, Milwaukee, WI); Hank's Buffer (Cellgro, Mediatech); Ethanol (Alcohol, dehydrated USP, Midwest Grain Products of Illinois, Grain Processing Corp., Muscarine, IA); and Tween 20 (ICI Surfactants, Wilmington, DE).

Ricinoleic acid (P-10 Acids, Cas Chem, Bayonne, NJ) was centrifuged for 30 minutes at 15,000 rpm to remove solids.

The following tables list the formulations prepared. The tables give detailed information on the ingredients and amounts and pH if appropriate.

The general procedure for preparing the microemulsions is as follows: weigh ingredients into reclosable container, shake and sonicate if necessary to remove bubbles.

TABLE 17

Formulations for Pluronic L44/oily phase/Hands buffer microemulsions containing different fatty acids or alcohols as the oily phase and partial substitution of Hands buffer with ethanol.

Formulation: PD0002-						
Ingredients	19E (%)	19F (%)	20E (%)	27A (%)	27B (%)	29A (%)
Pluronic L44	27.0	27.0	27.0	27.4	26.6	27
Hank Buffer	9.9	9.9	9.9	8.8	9.9	4.95
oleyl alcohol	63.1	0	0			
oleic acid	0	63.1	63.1			
linoleic acid	0	0	63.1	0	63.4	63.1
linolenic acid				0	63.4	63.1
ricinoleic acid				0	63.4	63.1
ethanol				0	0	4.95

TABLE 18

Formulations for Pluronic L44/fatty alcohol or acid/Hank's buffer containing oleyl alcohol, oleic acid or linoleic acid (PD0002-19E, 19F, 20E respectively), with a substitution of ethanol for part of the Hank's buffer, (PD0002-31A, 31B and 29A) and total substitution of Hank's buffer with ethanol (PD0002-31C) and a change in the ratio of Pluronic L44 to linoleic acid to 2:8 (PD0002-31D).

Formulation PD0002-31				
Ingredients	A%	B%	C%	D%
Pluronic L44	27	27	27	19
Hank's buffer	4.95	4.95	N/A	5.1
oleyl alcohol	63.1	N/A	N/A	75.9
oleic acid	N/A	63.1	N/A	N/A
linoleic acid	N/A	N/A	63.1	N/A
ethanol	4.95	4.95	9.9	N/A

TABLE 19

Formulations of Pluronic L44/linoleic acid/Hank's buffer with varying substitutions of ethanol (PD0002-50A through J) and Pluronic L44/oleyl alcohol/Hank's buffer with ethanol substitutions (PD0002-65).

Formulation PD0002-50						
Ingredients	A	B	C	D	E	F
Pluronic L44	27	27	27	27	27	27
Hank's buffer	9.9	4.95	9.9	9.9	9.9	9.9
linoleic acid	63.1	63.1	54.1	58.6	49.6	45.1
ethanol	0	4.95	9	4.5	13.5	18.02

Formulation PD0002-50				
Ingredients	G	H	I	J
Pluronic L44	27	27	27	27
Hank's buffer	9.9	9.9	9.9	9.9
linoleic acid	40.54	36	31.5	27
ethanol	22.52	27	31.5	36

Formulation PD0002-65	
Ingredients	A
Pluronic L44	27.03
Hank's buffer	9.91
oleyl alcohol	54.04
ethanol	9.01

TABLE 20

Addition of water soluble surfactants SLS, sodium cholate and Tween 20 (PD0002-32 A, B, and C, respectively) and addition of an oil soluble additive Eastman SAIB (PD0002-34B) to microemulsion.

Formulation PD0002				
Ingredients	32 A%	32 B%	32 C%	34 B%
Pluronic L44	27	27	27	27
Hank's buffer	9.9	9.9	9.9	9.9
linoleic acid	63	63	63	63
Solium Lauryl Sulfate	0.1	N/A	N/A	N/A
sodium cholate	N/A	0.1	N/A	N/A
Tween 20	N/A	N/A	0.1	N/A
Eastman SAIB				0.111

Formulation	Ingredients		
PD0002-30	Pluronic	% Pluronic	% Hank's buffer
A	L35	0.5	95
B	L61	0.5	95
C	L62	0.5	95
D	L64	0.5	95
E	L35	1	90
F	L61	1	90
G	L62	1	90
H	L64	1	90
I	L44/L61	0.25/0.25	95
J	L44/L61	0.5/0.5	90
K	L44	5	95

TABLE 21

Substitutions of Pluronic L44 with L64 and L35 in the microemulsion formulations.

Formulation PD0002-33		
Ingredients	A %	B %
Pluronic L64	27	N/A
Hank's buffer	9.9	9.9
linoleic acid	63.1	63.1
Pluronic L35	N/A	27

TABLE 22

Pluronic L62/linoleic acid/Hank's buffer microemulsion.

Formulation PD0002-41E	
Ingredients	%
Pluronic L62	42.87
Hank's buffer	14.4
linoleic acid	42.8

What Is Claimed Is:

1. A pharmaceutical preparation comprising a stable emulsion of a pharmaceutical agent incorporated into a hydrophobic emulsion of a long chain carboxylic acid, long chain carboxylic acid ester, long chain carboxylic acid alcohol and mixtures thereof in a dosage form suitable for oral delivery.

2. The pharmaceutical preparation of claim 1 wherein the emulsion or dispersion is a microcolloidal emulsion.

3. The pharmaceutical preparation of claim 1 wherein the long chain carboxylic acid is selected from the group consisting of n-dodecanoic acid, n-tetradecanoic acid, n-hexadecanoic acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, montanic acid, melissic acid, oleic acid, gadoleic acid, erucic acid, linoleic acid, linolenic acid, arachidonic acid, behenolic acid and diacetyl tartaric acid.

4. The pharmaceutical preparation of claim 1 wherein the long chain carboxylic acid ester is selected from the group consisting of glyceryl monostearates; glyceryl monopalmitates; mixtures of glyceryl monostearate and glyceryl monopalmitate; glyceryl monolinoleate; glyceryl monooleate; mixtures of glyceryl monopalmitate, glyceryl monostearate, glyceryl monooleate and glyceryl monolinoleate; glyceryl monolinolenate; glyceryl monogadoleate; mixtures of glyceryl monopalmitate, glyceryl monostearate, glyceryl monooleate, glyceryl monolinoleate, glyceryl monolinolenate and glyceryl monogadoleate; acetylated glycerides such as distilled acetylated monoglycerides; mixtures of propylene glycol monoesters, distilled monoglycerides, sodium stearoyl lactylate and silicon dioxide; mixtures of propylene glycol

monoesters, distilled monoglycerides, sodium stearoyl lactylate and silicon dioxide; d-alpha tocopherol polyethylene glycol 1000 succinate; mixtures of mono- and di-glyceride esters; calcium stearoyl lactylate; ethoxylated mono- and di-glycerides; lactated mono- and di-glycerides; lactylate carboxylic acid ester of glycerol and propylene glycol; lactylic esters of long chain carboxylic acids; polyglycerol esters of long chain carboxylic acids, propylene glycol mono- and di-esters of long chain carboxylic acids; sodium stearoyl lactylate; sorbitan monostearate; sorbitan monooleate; other sorbitan esters of long chain carboxylic acids; succinylated monoglycerides; stearyl monoglyceryl citrate; stearyl heptanoate; cetyl esters of waxes; stearyl octanoate; C_{10}-C_{30} cholesterol/lavosterol esters; and sucrose long chain carboxylic acid esters.

5. The pharmaceutical preparation of claim 1 wherein the hydrophobic emulsion comprises a self-emulsifying surface-active hydrophobic material.

6. The pharmaceutical preparation of claim 5 wherein the self-emulsifying hydrophobic material is selected from the groups of stearates, palmitates, ricinoleates, oleates, behenates, ricinolenates, myristates, laurates, caprylates, and caproates.

7. The pharmaceutical preparation of claim 1 wherein the long chain carboxylic acid alcohol is selected from the group consisting of n-dodecanoic acid alcohol, n-tetradecanoic acid alcohol, n-hexadecanoic acid alcohol, caproic acid alcohol, caprylic acid alcohol, capric acid alcohol, lauric acid alcohol, myristic acid alcohol, palmitic acid alcohol, stearic acid alcohol, arachidic acid alcohol, behenic acid alcohol, montanic acid alcohol, melissic acid alcohol, oleic acid alcohol, gadoleic acid alcohol, erucic

acid alcohol, behenolic acid alcohol and diacetyl tartaric acid alcohol.

8. The pharmaceutical preparation of claim 1 which further conprises a surfactant present in a range of about 0.05% to 2.0% weight/weight of the hydrophobic composition.

9. The pharmaceutical preparation of claim 8 wherein the surfactant is selected from the group consisting of polyoxyethylene sorbate long chain carboxylic acid ester surfactants, sorbitan long chain carboxylic acid ester surfactants, ethylene or propylene oxide block copolymer surfactants, polyglycolyzed glyceride surfactants, sorbitan esters of oleate, stearate, laurate or other long chain carboxylic acids, poloxamers, other sorbitan or sucrose long chain carboxylic acid esters, mono and diglycerides, PEG derivatives of caprylic/capric triglycerides and mixtures thereof.

10. The pharmaceutical preparation of claim 1 wherein the pharmaceutical agent has less than about 80% bioavailability.

11. The pharmaceutical preparation of claim 1 wherein the pharmaceutical agent is a polypeptide of up to about 15 amino acids.

12. The pharmaceutical preparation of claim 11 wherein the polypeptide of up to about 12 amino acids.

13. The pharmaceutical preparation of claim 1 wherein the pharmaceutical agent is an organic molecule of less than about 1,000 daltons.

14. The pharmaceutical preparation of claim 13 wherein the organic molecule is less than about 600 daltons.

15. The pharmaceutical preparation of claim 1 wherein the pharmaceutical agent is selected from cyclosporin, angiotensin I, II and III, encephalins, enkephalins and their analogs, ACTH, antiinflammatory peptides I, II, III, bradykinin, calcitonin, cholecystokinin fragments 26-33 and 30-33, pre/pro cholecystokinin (V-9-M), ß-endorphin, dinorphin, leucokinin, leutinizing hormone releasing hormone, neurokinins, somatostatin, substance P, thyroid releasing hormone, vasopressin, fibrinogen receptor antagonists (arginine-glycine-aspartic acid containing peptides) which are platelet aggregation inhibitors, growth hormone releasing peptides (GHRP), insulin, LH-RH releasers and inhibitors, endothelins, cholecystokinin, atrial natreuretic factor, gastrin, cytoprotectives, MSH modulators, elastase or renin inhibitors growth factors and cytokines, HIV protease inhibitors, cabamazepine, griseofulvin, angiotensin converting enzyme inhibitors, flutamide, nifedipine, acyclovir, gancyclovir, indomethacin, naproxen, estrogens, testosterones, steroids, phenytoin, ergotamines and cannabinoids.

16. The pharmaceutical preparation of claim 1 wherein the emulsion is encapsulated in a capsule comprising an enteric coating material.

17. The pharmaceutical preparation of claim 1 wherein the microcolloidal emulsion is encapsulated in a capsule that is soluble in an acidic aqueous environment.

18. The pharmaceutical preparation of claim 1 wherein the emulsion is encapsulated in a capsule comprising an enteric coating material.

19. The pharmaceutical preparation of claim 1 wherein the microcolloidal emulsion is encapsulated in a capsule that is soluble in an acidic aqueous environment.

20. A pharmaceutical preparation comprising a stable emulsion of a pharmaceutical agent incorporated into an emulsion having a hydrophilic discontinuous phase dispersed in a continuous phase of a long chain carboxylic acid, long chain carboxylic acid ester, long chain carboxylic acid alcohol and mixtures thereof in a dosage form suitable for oral delivery.

21. The pharmaceutical preparation of claim 20 wherein the emulsion or dispersion is a microcolloidal emulsion.

22. The pharmaceutical preparation of claim 20 wherein the long chain carboxylic acid is selected from the group consisting of n-dodecanoic acid, n-tetradecanoic acid, n-hexadecanoic acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, montanic acid, melissic acid, oleic acid, gadoleic acid, erucic acid, linoleic acid, linolenic acid, arachidonic acid, behenolic acid and diacetyl tartaric acid.

23. The pharmaceutical preparation of claim 20 wherein the long chain carboxylic acid ester is selected from the group consisting of glyceryl monostearates; glyceryl monopalmitates; mixtures of glyceryl monostearate and glyceryl monopalmitate; glyceryl monolinoleate; glyceryl monooleate; mixtures of glyceryl monopalmitate, glyceryl monostearate, glyceryl monooleate and glyceryl monolinoleate; glyceryl monolinolenate; glyceryl monogadoleate; mixtures of glyceryl monopalmitate, glyceryl monostearate, glyceryl

monooleate, glyceryl monolinoleate, glyceryl monolinolenate and glyceryl monogadoleate; acetylated glycerides such as distilled acetylated monoglycerides; mixtures of propylene glycol monoesters, distilled monoglycerides, sodium stearoyl lactylate and silicon dioxide; mixtures of propylene glycol monoesters, distilled monoglycerides, sodium stearoyl lactylate and silicon dioxide; d-alpha tocopherol polyethylene glycol 1000 succinate; mixtures of mono- and di-glyceride esters; calcium stearoyl lactylate; ethoxylated mono- and di-glycerides; lactated mono- and di-glycerides; lactylate carboxylic acid ester of glycerol and propylene glycol; lactylic esters of long chain carboxylic acids; polyglycerol esters of long chain carboxylic acids, propylene glycol mono- and di-esters of long chain carboxylic acids; sodium stearoyl lactylate; sorbitan monostearate; sorbitan monooleate; other sorbitan esters of long chain carboxylic acids; succinylated monoglycerides; stearyl monoglyceryl citrate; stearyl heptanoate; cetyl esters of waxes; stearyl octanoate; C_{10}-C_{30} cholesterol/lavosterol esters; and sucrose long chain carboxylic acid esters.

24. The pharmaceutical preparation of claim 20 wherein the hydrophobic emulsion comprises a self-emulsifying surface-active hydrophobic material.

25. The pharmaceutical preparation of claim 24 wherein the self-emulsifying hydrophobic material is selected from the groups of stearates, palmitates, ricinoleates, oleates, behenates, ricinolenates, myristates, laurates, caprylates, and caproates.

26. The pharmaceutical preparation of claim 20 wherein the long chain carboxylic acid alcohol is selected from the group consisting of n-dodecanoic acid alcohol, n-tetradecanoic acid alcohol, n-hexadecanoic acid alcohol,

caproic acid alcohol, caprylic acid alcohol, capric acid alcohol, lauric acid alcohol, myristic acid alcohol, palmitic acid alcohol, stearic acid alcohol, arachidic acid alcohol, behenic acid alcohol, montanic acid alcohol, melissic acid alcohol, oleic acid alcohol, gadoleic acid alcohol, erucic acid alcohol, behenolic acid alcohol and diacetyl tartaric acid alcohol.

27. The pharmaceutical preparation of claim 20 which further conprises a surfactant present in a range of about 0.05% to 2.0% weight/weight of the hydrophobic composition.

28. The pharmaceutical preparation of claim 27 wherein the surfactant is selected from the group consisting of sodium lauryl sulfate, polyoxyethylene sorbate long chain carboxylic acid ester surfactants, sorbitan long chain carboxylic acid ester surfactants, ethylene or propylene oxide block copolymer surfactants, polyglycolyzed glyceride surfactants, sorbitan esters of oleate, stearate, laurate or other long chain carboxylic acids, poloxamers, other sorbitan or sucrose long chain carboxylic acid esters, mono and diglycerides, PEG derivatives of caprylic/capric triglycerides and mixtures thereof.

29. The pharmaceutical preparation of claim 20 wherein the pharmaceutical agent has less than about 80% bioavailability.

30. The pharmaceutical preparation of claim 20 wherein the pharmaceutical agent is a polypeptide of up to about 15 amino acids.

31. The pharmaceutical preparation of claim 30 wherein the polypeptide of up to about 12 amino acids.

32. The pharmaceutical preparation of claim 20 wherein the pharmaceutical agent is an organic molecule of less than about 1,000 daltons.

33. The pharmaceutical preparation of claim 32 wherein the organic molecule is less than about 600 daltons.

34. The pharmaceutical preparation of claim 20 wherein the pharmaceutical agent is selected from cyclosporin, angiotensin I, II and III, encephalins, enkephalins and their analogs, ACTH, antiinflammatory peptides I, II, III, bradykinin, calcitonin, cholecystokinin fragments 26-33 and 30-33, pre/pro cholecystokinin (V-9-M), ß-endorphin, dinorphin, leucokinin, leutinizing hormone releasing hormone, neurokinins, somatostatin, substance P, thyroid releasing hormone, vasopressin, fibrinogen receptor antagonists (arginine-glycine-aspartic acid containing peptides) which are platelet aggregation inhibitors, growth hormone releasing peptides (GHRP), insulin, LH-RH releasers and inhibitors, endothelins, cholecystokinin, atrial natreuretic factor, gastrin, cytoprotectives, MSH modulators, elastase or renin inhibitors growth factors and cytokines, and HIV protease inhibitors, cabamazepine, griseofulvin, angiotensin converting enzyme inhibitors, flutamide, nifedipine, acyclovir, gancyclovir, indomethacin, naproxen, estrogens, testosterones, steroids, phenytoin, ergotamines and cannabinoids.

35. The pharmaceutical preparation of claim 20 wherein the emulsion is encapsulated in a capsule comprising an enteric coating material.

36. The pharmaceutical preparation of claim 20 wherein the microcolloidal emulsion is encapsulated in a capsule that is soluble in an acidic aqueous environment.

FIG. 1

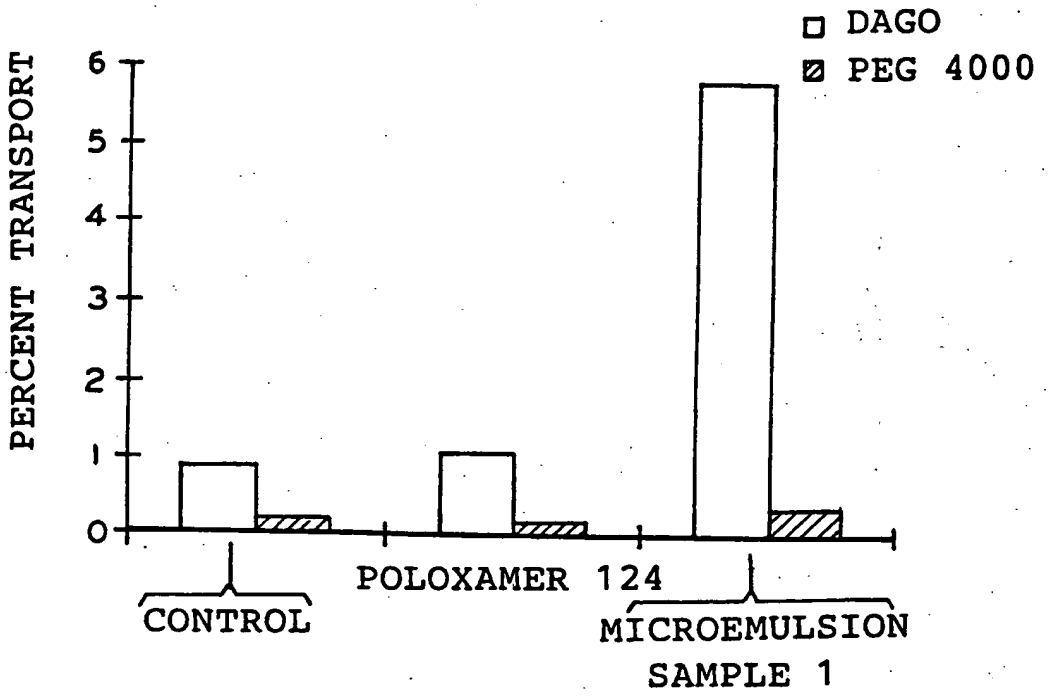


FIG. 2

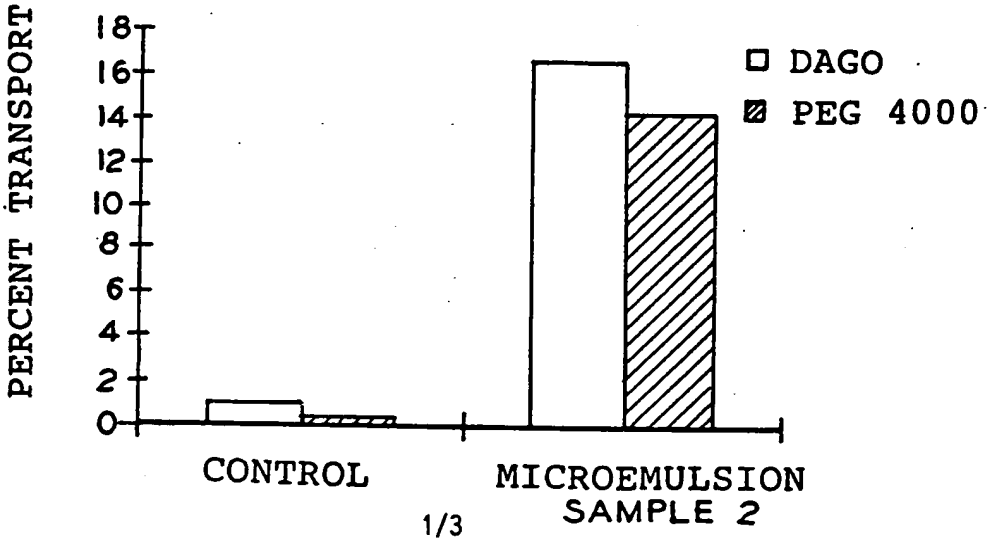


FIG. 3

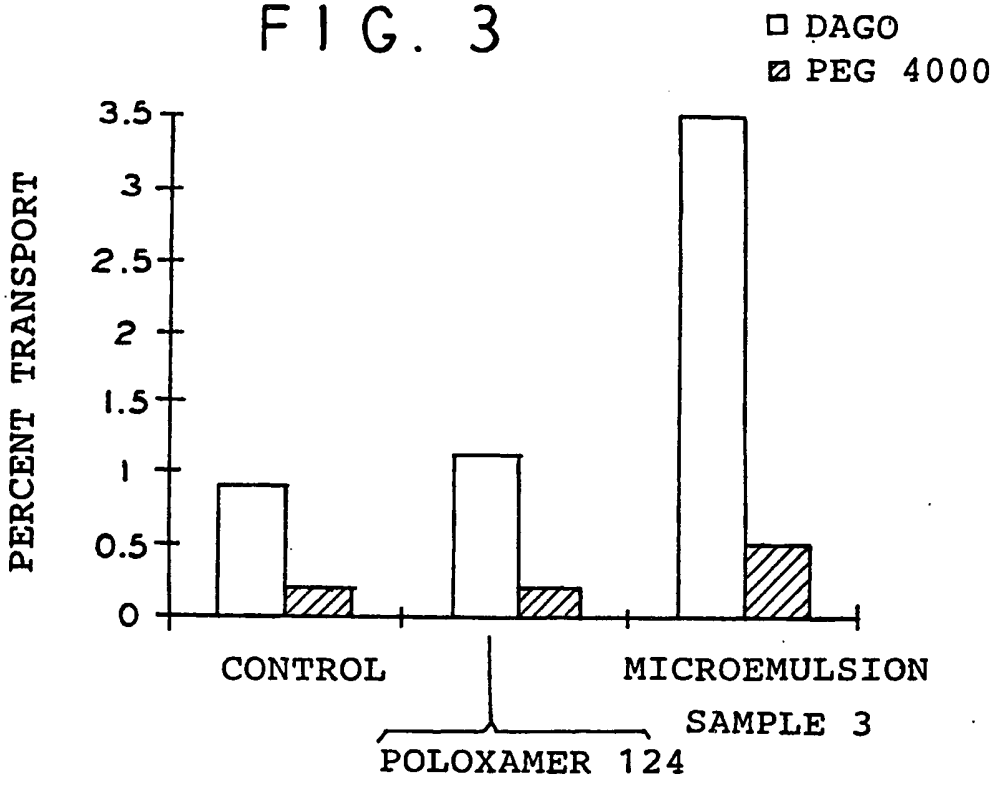

DAGO
PEG 4000
PERCENT TRANSPORT
3.5
3
2.5
2
1.5
1
0.5
0
CONTROL
MICROEMULSION
SAMPLE 3
POLOXAMER 124

FIG. 4

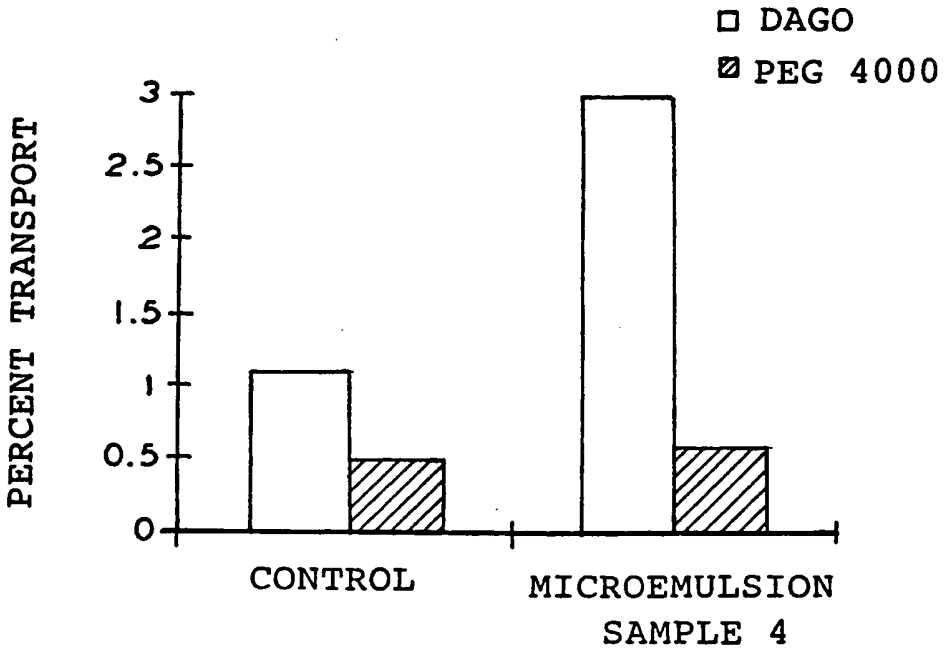
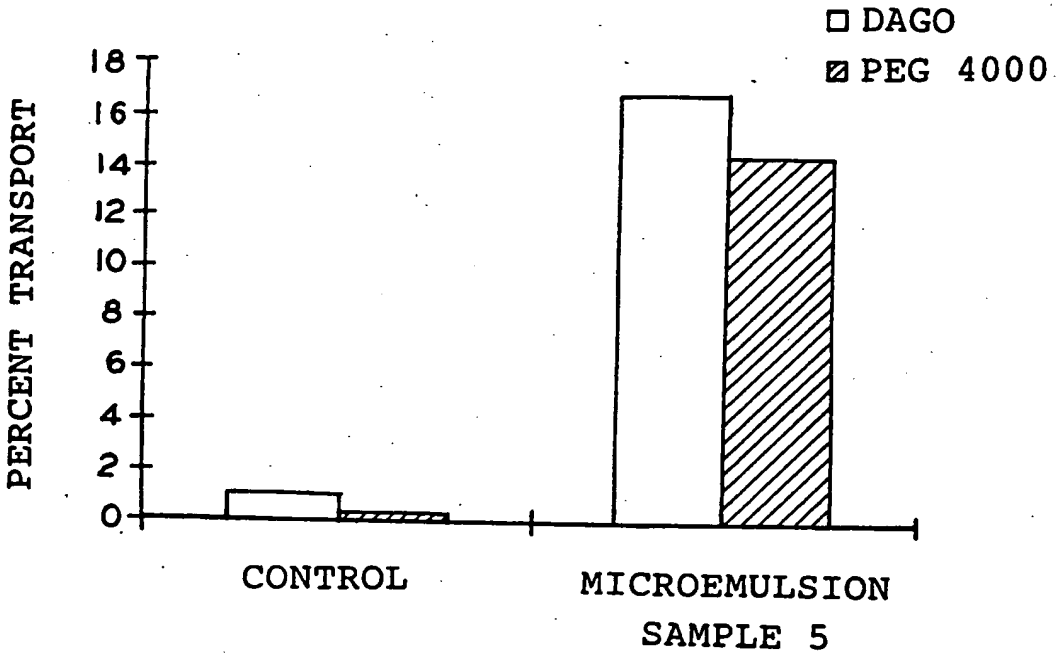

DAGO
PEG 4000
PERCENT TRANSPORT
3
2.5
2
1.5
1
0.5
0
CONTROL
MICROEMULSION
SAMPLE 4

FIG. 5


DAGO
PEG 4000
PERCENT TRANSPORT
18
16
14
12
10
8
6
4
2
0
CONTROL
MICROEMULSION
SAMPLE 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/03393

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/107
US CL :514/ 785, 786, 943
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/ 785, 786, 943

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS: emulsi?, acids/alcohols of claims 3-4

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,330,338 (BANKER et al) 18 May 1982, column 4.	1-10, 13, 14, 20-29, 32, 33
Y	US, A, 4,606,913 (ARONSON et al) 19 August 1986, columns 5-6, 14-16, 18.	1-10, 13, 14, 20-29, 32, 33
Y	US, A, 4,690,775 (SCHOTT et al) 01 September 1987, column 3.	1-10, 13, 14, 20-29, 32, 33
Y	US, A, 4,990,337 (KURIHARA et al) 05 February 1991, columns 3-5.	1-10, 13, 14, 20-29, 32, 33

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 12 JUNE 1995	Date of mailing of the international search report 03 JUL 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer S. MARK CLARDY Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/03393

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,122,543 (KHANNA) 16 June 1992, columns 1, 3-5.	1-10, 13, 14, 20-29, 32, 33
Y,P	US, A, 5,326,570 (RUDNIC et al) 05 July 1994, columns 1-3.	1-10, 13, 14, 20-29, 32, 33
Y,P	US, A, 5,342,625 (HAUER et al) 30 August 1994, columns 10-11.	1-10, 13, 14, 20-29, 32, 33

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/03393

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-10, 13, 14, 20-29, 32, 33 (7-member N-heterocycle (carbamazepine))

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/03393

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

I. Claims 1-10, 13, 14, 20-29, 32, and 33 drawn to compositions comprising a pharmaceutical agent emulsified in long chain carboxylic acids or esters classified in 514/785, 786, 943.

II. Claims 15 and 34, drawn to the compositions of Group I wherein the pharmaceutical agent comprises:

A. 7-member N-heterocycle (carbamazepine) classified in 514/217;

B. 6-member 2N-heterocycle (ergotamine, acyclovir, ganciclovir) classified in 514/249, 262;

C. 6-member 1N-heterocycle (i.e., nifedipine) classified in 514/356;

D. 5-member N-heterocycle (i.e., phenytoin, indomethacin) classified in 514/420;

E. O-heterocycle (cannabinol, griseofulvin) classified in 514/454, 473;

F. steroids, estrogens, and testosterones classified in 514/177-182;

G. aromatic acids/amides (naproxen, flutamide) classified in 514/571, 629;

H. cyclopeptides classified in 514/9;

I. polypeptides of more than about 15 amino acids classified in 514/12-13.

III. Claims 11, 12, 15, 30, 31, and 34 drawn to compositions of Group I wherein the active agent is a polypeptide comprising up to about 15 amino acids classified in 514/14-18.

IV. Claims 16, 18, and 35 drawn to the emulsions of Group I in a capsule comprising an enteric coating material classified in 424/463.

V. Claims 17, 19, and 36 drawn to the emulsions of Group I in a capsule which is soluble in an acidic aqueous environment classified in 424/455.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows: I, IIa-IIi, III, IV, and V, above.

The following claims are generic: 1, 20.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: PCT Rules 13.1 and 13.2 do not provide for multiple products. The species are drawn to pharmaceutical agents which are diverse both structurallyand functionally.